INTRODUCTION OF AQUEOUS CHEMISTRY AND OUTLINE OF THESIS

Introduction:

It is widely acknowledged that there is growing need for more environmentally acceptable processes in the chemical industry. This trend towards what has become known as ‘Green Chemistry’ or ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

A reasonable working definition of green chemistry can be formulated as follows: green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

Chemistry is undeniably a very prominent part of our daily life. Food and drink has been made safe to consume, the development of cosmetics has enabled us to beautify and admire our appearances and the whole area of pharmaceuticals has allowed the development and synthesis of new cures for illnesses and diseases, all as a result of chemistry. However, in the chemical industry, solvents are used in large quantities. In particular, in fine-chemical and pharmaceutical production, large amounts are used for final products. Therefore, solvents define a major part of the environmental performance of a process and also impact on cost, safety and health issues as well as the continuously increasing air pollution has brought about changes in the global climate. The idea of “green” solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production. Recently, four directions towards green solvents have been developed:

(i) Substitution of hazardous solvents with ones that show better EHS (environmental, health and safety) properties, such as increased biodegradability or reduced ozone depletion potential\(^\text{1-3}\) (ii) Use of “bio-solvents,” i.e. solvents produced with renewable resources such as ethanol produced by fermentation of sugar-containing feeds, starchy feed materials or lignocelluloses materials\(^\text{4}\) (this substitution of petrochemically fabricated solvents leads to an avoidance of fossil resource use and fossil fuel CO\(_2\) emissions to the environment); (iii) Substitution of organic solvents either with supercritical fluids that are environmentally harmless (e.g. the use of supercritical CO\(_2\) in polymer processing\(^\text{5-8}\) avoids the use of chlorofluorocarbons, and thus reduces ozone
depletion); (iv) Use of non-volatile and thermally stable ionic liquids as solvents in the place of traditional industrial solvents, most of which are volatile organic compounds (VOCs). Replacement of conventional solvents by water would prevent the emission of VOCs, a major source of environmental pollution. Water can be designed to be environmentally benign, with large potential benefits for sustainable chemistry.

A green solvent must ideally have negligible vapour pressure, high boiling point, be nontoxic, have capacity to dissolve wide range of organic, inorganic and organometallic compounds, it should be chemically and physically stable, recyclable, reusable, inexpensive and eventually easy to handle. In addition to these, solvents that allow more selective and rapid transformations will have a significant impact. Therefore, many attempts have been made to substitute conventional organic solvents with novel alternative reaction media, which include: supercritical fluids, per fluorinated solvents, low melting polymers, ionic liquids and more particularly water.

A. Alternative solvents in organic synthesis

1. Supercritical fluids

A supercritical fluid (SCF) is defined as a substance above its critical temperature (Tc) and critical pressure (Pc). Supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years. Several features of scCO₂ make it an interesting solvent in the context of green chemistry and catalysis. The critical pressure and temperature for carbon dioxide are moderate (74 atm and 31.1 °C) and these conditions are easily achieved in laboratory. Thus the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is nontoxic, chemically inert towards many substances, nonflammable, and simple depressurization results in its removal. It is miscible with, e.g. hydrogen, making it an interesting solvent for hydrogenation and hydroformylation. Furthermore, the physical properties of scCO₂, e.g. polarity, can be tuned by manipulation of the temperature and pressure. Although it is a greenhouse gas its use involves no net addition to the atmosphere; it is borrowed as it were. Its main uses are as a replacement for VOCs in extraction processes. For example, it is widely used for the decaffeination of coffee where it replaced the use of a chlorinated hydrocarbon.

2. Poly(ethylene glycol) – PEG

Poly (ethylene glycol) is the linear polymer formed from the polymerization of ethylene oxide. PEG usually indicates the polyether of molecular weight less than 20,000 and is
known to be inexpensive, thermally stable, recoverable, biologically compatible and nontoxic. Furthermore, PEG and its monomethylethers have a low vapor pressure, are nonflammable, present simple workup procedures and can be recycled. For these reasons PEG is considered to be an environmentally benign alternative to chemical volatile solvents and a highly practical medium for organic reactions. PEG is most commonly employed as support for various transformations (PEG 2,000-20,000)\(^{10}\) and as a biologically acceptable polymer used extensively in drug delivery and bioconjugates as tools for diagnostics but it can also be employed as an efficient medium for phase transfer catalysts. Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. One of the major drawbacks in its use in organic reactions that also applies to ionic liquids is the inconvenience of using organic solvents to extract the products, even though scCO\(_2\) can also be used in both cases. Probably due to the higher popularity of other alternative solvents, especially ionic liquids, there are only a few examples in the literature that uses PEG as solvent in organic reactions.

3. Perfluorinated (fluorous) solvents

The fluorous compounds were defined as being compounds that are highly fluorinated and based upon sp3-hybridized carbons. Fluorous (perfluorinated) solvents as perfluoroalkenes, perfluoralkyl ethers and perfluoroalkylamines are generally chemically benign and environmentally-friendly for being non-toxic (unlike the freons), nonflammable, thermally stable, recyclable, and for their high ability to dissolve oxygen gas, which is an advantage used in medical technology. Fluorous fluids have very unusual properties, such as high density and high stability (mainly due to the stability of the C-F bond), low solvent strength, and extremely low solubility in water and organic solvent,\(^{11}\) although they are miscible at higher temperature. The poor solubility of fluorinated solvents can be explained based on their low surface tensions, low intermolecular interactions, high densities and low dielectric constants. The manufacture of these fluorous solvents is not so simple generally requiring the use of huge amounts of high volatile organic solvents and toxic reagents such as fluorine gas and HF.

4. Ionic liquid

In the past two decades, ionic liquids have been widely used as “green solvents” replacing traditional organic solvents for organic synthesis and catalysis. The great interest for such compounds relies on the fact that they posses several attractive properties such as negligible vapor pressure, chemical and thermal stability, nonflammability, high ionic conductivity,
wide electrochemical potential window and moreover the ability to act as catalysts. In contrast to conventional solvents that are constituted of molecules, ionic liquids consist of ions and are liquid at room temperature (RTILs) or have a low melting point (generally below 100°C). This ionic character allows them to potentially behave in a very different manner when used as solvents as compared to conventional molecular liquids.

By changing the anion or alkyl chain of the cation, one can vary physical properties such as the hydrophobicity, viscosity, density, and solvation of the ionic liquid system. For this reason they have been referred to as “designer solvents”12. ILs can be easily separated from the organic products of a reaction but this process usually requires extraction with a non polar organic solvent. Their high viscosities make stirring and homogenization of the reaction medium difficult, which causes slow dissolution of solids. Other drawbacks are their higher costs as compared to most organic solvents and also little is known about their toxicity.

5. Water

Water is perhaps one of the greener solvents one can imagine in terms of costs, availability, safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow13 and Grieco14 in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. For instance, the rates and stereoselectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic co-solvents or surfactants helps to increase the solubility of nonpolar reactants in water by disrupting the strong hydrogenbond network of pure water.15 The discovery that Lewis acids, especially some metal triflates, can efficiently catalyze reactions in water also contributed to popularize it as solvent in organic reactions.16

B. Brief history of water

1. Water as solvent (Why water?)

Until recently, the use of water as solvent for organic reactions was mainly restricted to simple hydrolysis reactions. Accordingly, most reagents and catalysts in organic synthesis have been imperiously developed for use in anhydrous, organic reaction media.
Why should we now spend time "rediscovering" reactions for use in water that already work well in familiar organic solvents such as THF, toluene, or methylene chloride? Because there are many potential advantages of replacing these and other unnatural solvents with water. The most obvious are the following. (1) Cost. It does not get any cheaper than water! (2) Safety. Most of the organic solvents used in the lab today are associated with risks: Flammables, explosives, carcinogens, etc. (3) Environmental concerns. The chemical industry is a major contributor to environmental pollution. With increasing regulatory pressure focusing on organic solvents, the development of nonhazardous alternatives is of great importance.

It is, however, important that the above listed benefits are not gained at the expense of synthetic efficiency. Even a small decrease in yield, catalyst turnover, or selectivity of a reaction can lead to a substantial increase in cost and amount of waste generated. Fortunately, many theoretical and practical advantages of the use of water as solvent for organic synthesis do exist. These will be elaborated upon below but are briefly introduced here. First, experimental procedures may be simplified since isolation of organic products and recycling of water-soluble catalysts and other reagents could be made by simple phase separation. Second, laborious protecting-group strategies for functionalities containing acidic hydrogens may be reduced. Third, water-soluble compounds could be used in their "native" form without the need for hydrophobic derivatization, again eliminating tedious protection-deprotection steps from the synthetic route. Fourth, as will be amply exemplified in this review, the unique solvating properties of water have been shown to have beneficial effects on many types of organic reactions in terms of both rate and selectivity.

2. The unusual behavior of water as a solvent

Water is, undoubtedly, the most intensively studied solvent. Its abundance is a prerequisite for life; some of the unusual properties of water are directly reflected in the organization of living matter.\(^{17}\) In fact, it is difficult if not impossible to imagine another liquid that is suitable for complicated self-assembly and supramolecular organization to the extent and variation observed in water. The large number of unusual properties of water distinguishes it from ‘normal’ liquids.\(^{18}\) The molecule is small and interacts with other water molecules mainly by strong, directional hydrogen bonds (10–40 kJ mol\(^{-1}\) each),\(^{19}\) resulting in an unusually high boiling point for such a small molecule (e.g. NH\(_3\), HF, and H\(_2\)S are all gases at room temperature (RT) and 1 atm.). However, the number of self-interactions; i.e., water-water interactions, is low (4 in the
solid state, ca. 4–5 in liquid RT water). Aqueous chemistry often differs from non-aqueous chemistry because of these features. In particular, hydrophobic effects distinguish water from other solvents.

Many (inorganic) salts that are only slightly soluble in organic solvents are highly soluble in water. When a salt dissolves, ion-ion interactions in the solid are broken. However, the accompanying loss in energy is in part compensated by relatively strong interactions of ions with polar water molecules. On the other hand, the solubility of hydrocarbons in water is limited. It was suggested very early in the literature, that water is a poor solvent for hydrocarbons because the water-water interactions are strong, and both hydrocarbon-hydrocarbon and hydrocarbon-water interactions are weak (hydrocarbons interact mainly by dispersion interactions, ≈ 1 kJ mol⁻¹ ‘each’). When thermodynamic data became available, the complete picture turned out to be more complicated, which led to a large number of studies dealing with the hydration of apolar structures. In the following sections, origins and consequences of this so-called ‘hydrophobic hydration’ are discussed.

**Hydrophobic hydration**

Hydrophobic interactions (HI) between apolar molecules or apolar parts of molecules in water have been studied since the last part of the nineteenth century. These interactions are of paramount importance in chemistry. Aggregation of phospholipids and other lipid components in biological cell membranes is driven by HI and HI also play a crucial role in protein folding and often in enzyme–substrate interactions. There are, however, numerous other processes in aqueous solution in various chemical disciplines, which depend strongly on HI.

HI are different from all other noncovalent interactions in the liquid phase in the sense that they do not primarily depend on direct attractive intermolecular interactions between the species that are perceived to interact but are rather driven by the tendency of water molecules to retain their own water–water hydrogen-bond interactions as much as possible, leading to a tendency to arrange nonpolar entities such that the contact surface area between these and water is minimised.

The precise mechanism of HI has been under debate for many decades and still all details are not well understood. Particularly the thermodynamics of dissolution of apolar molecules in water and of HI have been discussed extensively and it is only recently that consistent interpretations have been advanced. Much of our current insight is derived from fundamental studies on the transfer thermodynamics of small
nonpolar molecules from the gas phase to water, providing information on the way
water molecules arrange themselves around nonpolar entities (i.e. hydrophobic
hydration).28
At room temperature apolar molecules are warmly received (strongly negative enthalpy
of transfer) upon transfer from the gas phase to water, yet the Gibbs energy is strongly
positive due to a dominating large and unfavourable entropic contribution. For many
years it was believed that the hydrophobic hydration shells are characterised by a
strengthening of water–water hydrogen bonding (more or stronger hydrogen bonds) per
volume unit as compared with bulk water. This effect was often described as an increase
in “water structure”.
Recent rather compelling evidence (neutron scattering, NMR, MD simulations,
quantum chemistry, thermodynamics) 25 suggests that this picture for hydrophobic
hydration needs
revision. Upon dissolution of relatively small nonpolar molecules at room temperature,
the water molecules surrounding the nonpolar surface tend to keep their hydrogen-
bonding network largely intact. Since the nonpolar surface cannot donate or accept
hydrogen bonds, this leads to a tendency for tangential orientation of the water O–H
bonds relative to the apolar surface (Fig. 1). This preference for water orientation most
likely offers the explanation for the substantial loss of entropy upon transfer of apolar
groups or molecules from the gas phase to water.
However, this preference to maintain hydrogen bonds does not appear to be a strong
one. Increase in temperature will lead to progressive breaking of hydrogen bonds in the
hydrophobic hydration shell, with the transfer of nonpolar molecules from the gas phase
to water eventually becoming enthalpically rather than entropically unfavorable.
Cosolutes can lead to a similar shift towards a dominating enthalpy term. Similarly,
increasing the size and decreasing the curvature of the nonpolar species makes it
increasingly difficult to maintain an extensively hydrogen-bonded hydrophobic
hydration shell. Hydration of a flat nonpolar surface is inevitably characterised by
dangling hydrogen bonds; an arrangement which is even more prevalent in the
hydration of nonpolar cavities. For instance, the binding through HI of nonpolar
molecules inside the cavity of cyclodextrin receptors is usually enthalpy driven.
HI are driven by the favorable rearrangement of water molecules that can occur upon
bringing nonpolar entities together and HI is essentially a partial reversal of the process
of hydrophobic hydration. Where for the formation of the hydrophobic hydration shell water molecules need to be recruited from the bulk solvent, HI are accompanied by the release of water molecules from the hydrophobic hydration shells back into bulk solution. Therefore the same factors that cause the thermodynamic signature for hydrophobic hydration to vary from entropy-driven to enthalpy-driven (temperature, cosolutes, size, and curvature of the solute) can cause HI to shift from being entropy driven to enthalpy driven.

Upon increasing the concentration of a nonpolar solute to a certain (perhaps critical) concentration, the relatively extensive hydrophobic hydration shells start to overlap destructively, which is accompanied by a release of water molecules from the hydrophobic hydration shell to the bulk aqueous medium. The apolar molecules, which are now in contact with each other, possess a smaller water-accessible surface area than the separate molecules and the release of the waters from their hydrophobic hydration shells provides the driving force for HI. Of course this whole solvent-induced association process is more complex because the two-apolar molecules also interact with each other by London dispersion forces. In order to get a more complete overview of HI, the reader is referred to the recent literature.25-28

HI can lead to pairwise interactions (short-lived 1:1 association, “encounter complexes”), to well-defined host-guest complexes, to the formation of small clusters of molecules (moving units), or to the formation of large aggregates (“bulk HI”; micelles, vesicles, etc.). It is clear that HI are associated with a complex interparticle potential that depends on the size27 and shapes30 of the molecules, on the temperature and pressure, and on the presence of cosolutes.
3. Solubility of organic compounds in water
Most chemical reactions are performed in solvents. The solvent provides a reaction medium in which reactants can be mixed over a very wide concentration range. In general, a good solvent should readily dissolve all or most of the participating reactants, should not interact adversely with the reaction, and should be easily separated during workup for facile isolation of products. On the basis of his/her knowledge of the chemical properties of the reactants, the chemist chooses a solvent, which is suitable to meet these criteria. From this perspective, it is not surprising that water has found limited use as solvent for organic reactions. In truth, the poor solubility of reactants and the deleterious effect on many organic transformations are the main obstacles to the use of water as reaction solvent. Nonetheless, the fact that many of the most desirable target molecules, e.g., carbohydrates, peptides, nucleotides, and their synthetic analogues, as well as many alkaloids and important drugs are readily soluble in water is inconsistent with the disproportionate bias toward the use of organic solvents for their preparation. It can be argued that our shortcomings as synthetic chemists prompt the use of exhaustive protecting group strategies, thus limiting the possibility of using water as solvent because of low solubility of the reactants. Moreover, with the limited arsenal of organic transformations in water that is presently available to the synthetic chemist, intermediates soluble in organic solvents are preferred to those soluble in water, even if it means adding extra synthetic steps for derivatization. This may have particular relevance in carbohydrate chemistry.

Notwithstanding the above, many organic targets and their intermediates have very low solubility in water, which may lead to thwarting of reactions due to phase separation and inefficient mixing of reactants, although heterogeneous mixtures may retain at least partly the positive influence of water, sometimes with the aid of sonication or microwave heating. A variety of strategies have been investigated in order to expand the scope of water-based organic synthesis to embrace also highly hydrophobic reactants, and these will be briefly discussed below. For a more comprehensive treatise, a thorough review of solubility and solubilization in aqueous media was recently published by Yalkowsky.\textsuperscript{31}

4. Water as a reaction medium
The limited solubility of many organic compounds explains why water traditionally has not been a popular solvent among organic chemists. Furthermore, many transformations involve reactive intermediates, which often readily react with water. However, alternative
routes to synthesize a particular compound may exist. The many complicated molecules that are found in living matter are all ‘bio-synthesized’ under aqueous conditions. Moreover, reaction conditions invariably are mild: ambient pressure, temperature and pH. One of the challenges of organic chemistry is to imitate nature in this respect.

Nowadays, many reactions have been successfully performed in water or a highly aqueous solvent mixture. Among these reactions are Michael additions, aldol reactions, epoxidations, reductions, Grignard- and Barbier-type reactions, Diels-Alder (DA) reactions, Heck reaction, Suzuki Reaction, and Sonogashira reaction.

C. Thesis outline

The main purpose of this study is to initiate aqueous media research in order to fill the gap in the craving research area and to advance our knowledge about aqueous media.

Chapter 1 describes the development and psychometrical evaluation of the Suzuki and Heck coupling reaction using water-soluble Sodium 2-(2-pyridin-3-yethylamino)sulfonate (N-donor ligand) in aqueous media. In this, we used Sodium 2-(2-pyridin-3-yethylamino)sulfonate as ligand as well as base for Suzuki and Heck reaction at room temperature. We also describe the role of suitable amount of co-solvent in the aqueous phase and reuse of palladium catalyst (section B).

Chapter 2 describes the novel, efficient, and green procedure for the synthesis of 1, 5-benzodiazepines catalyzed by MgBr₂,OEt₂ in water. In the same chapter, we also developed the selective synthesis of 2-arylbenzothiazoles and 2-arylbenzoxazoles using Alum (KAl(SO₄)₂·12H₂O) as catalyst in aqueous media.

Chapter 3 addresses the synthesis of 1,2-disubstituted benzimidazoles using glyoxylic acid as catalyst in aqueous media and we also describes the phosphomolybdic acid promoted synthesis of 2-substituted benzimidazoles in aqueous media. In the same chapter, we addressesaza-michael addition reaction using Sodium 2-(2-pyridin-3-yethylamino)sulfonate (N-donor ligand) as catalyst in water.

Chapter 4 presents practical and green approach towards synthesis of 1,5-benzodiazepines using cesium fluoride as efficient catalyst. Section B describes convenient and efficient method for the bromination of benzylic and aliphatic alcohols by using KBr/(COOH)₂ in aqueous media.
References:

20. The high relative permittivity of water affects the ion-ion, as well as the ion-dipole interactions.